REMARKS

Claims 1-12 have been rejected under 35 U.S.C. 112, second paragraph. Applicants have amended the claims to address the Examiner's comments. No new matter has been added.

Claims 7-12 have been rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification. Applicants respectfully traverse this rejection.

With regard to how that present invention is useful for treating neurological and neurobehavioral disorders, the Applicants present the following description and analysis of why one of ordinary skill in the art would agree that the provided evidence supports such uses.

Applicants describe some of the reported actions of thyrotropin-releasing hormone (TRH) and indicate some of the attributes of the endogenously occurring TRH analog, pGlu-Glu-Pro-amide that endow it with enhanced neuroprotective potential.

TRH was shown to improve neurological outcomes after experimental spinal cord injury and head injury in animals (Faden et al., 1989), and has been considered as a potential treatment for neurodegenerative diseases. In the office action, the Examiner refers to Patel (J. Geriatric Psychiatry and Neurology, vol 8: 81-95, April, 1995). Patel, in fact points out that "TRH exerts a positive neuromodulatory effect on the cholinergic system", and administered to patients with Alzheimer's Disease (AD) was shown to be safe and "produced modest improvement in arousal and semantic memory when administered on its own".

Newer art, however, does not accord with Patel's assertion that because this tripeptide crosses the blood brain barrier, it is a suitable agent for treatment of AD. It is now known that peripherally administered TRH is attacked and degraded in the bloodstream by the enzyme thyroliberinase and has a serum half life of only 5.3 minutes (Marangell et al., 1997). This severely limits the capacity of parenterally administered TRH to penetrate the CNS.

In marked contrast to TRH, pGlu-Glu-Pro-amide is not attacked by thyroliberinase (Pekary et al., 2000; O'Cuinn, 1995) and administered peripherally, does

in fact enter the brain, where levels remain elevated for hours (Pekary et al., 1999). It is known that pGlu-Glu-Pro-amide is present in the hippocampus, a part of the brain which is essential for important aspects of memory. The inventors have shown that pGlu-Glu-Pro-amide is as much as four times more effective as a neuroprotectant than TRH (Koenig et al., 2001) in neurons derived from brain or spinal cord .

The fact that pGlu-Glu-Pro-amide enters the brain more readily than does TRH and is superior to TRH in neuroprotective capacity (Koenig et al., 2001) should be entirely persuasive to one skilled in therapeutic arts that it specifically would be therapeutically beneficial in attenuating the progression of and ameliorating symptoms of chronic neurodegenerative diseases affecting the CNS, such as AD, Parkinson's Disease (PD), age-related macular degeneration (AMD) and amyotrophic lateral sclerosis (ALS).

After acute injury to any part of the central nervous system, a shadow or penumbra of spreading secondary injury often forms. An intervention after the primary injury may prevent secondary injury, thus limiting morbidity and mortality. For the same reasons that one expects pGlu-Glu-Pro-amide would be neuroprotective in chronic neurodegenerative diseases, it would also be expected by one of ordinary skill to be beneficial in attenuating neurotoxicity secondary to acute neurotrauma such as stroke, traumatic brain injury, spinal cord injury and retinal trauma (e.g. via laser exposure, accidental, therapeutic or during warfare).

The period of administration would range from 12 to 24 or 48 hours post injury in the case of spinal cord injury, to weeks in the case of stroke, to 6 months in the case of head injury or laser injury to the retina, where a chronic reaction may occur. Administration could be as frequent as every 4 hrs.

On page 4 of the office action, the Examiner raises the issue of nervous system regeneration. While specifically addressing neural de-generation, the Applicants have not specifically addressed re-generation. While not ruling out that pGlu-Glu-Pro-amide might exert a trophic effect enhancing neural regeneration or connectivity, the Applicants have not made that specific claim at this juncture.

Claims 1-2 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Cremades, et al. Applicants respectfully traverse this rejection.

Claim 1 has been amended to state that the pharmaceutical composition contains a neuroprotectant amount of pGlu-Glu-Pro-amide. The composition recited in Cremades et al. does not disclose a neuroprotectant amount. In fact, it states that "Our understanding of their physiological roles, however, is not yet complete. The "100μg in 300μl of aqueous solution" is an amount stated to have been used test plasma levels of T3 and T4. Cremades et al. does not state that this amount is neuroprotectant.

On p. 8 & 9 of the Office Action, the Examiner asserts that the Cremades paper (Eur. J. Pharm. 358:63-67, 1998) anticipates the claimed invention. The examiner states on p.9 that Cremades et al. teach that pGlu-Glu-Pro-amide was effective in "increasing levels of triiodothyronine and tetraiodothyronine when administered subcutaneously to mice" and refers to p. 64.

Applicants respectfully note that Table 1, on p. 64 of Cremades et al. actually shows that administration of pGlu-Glu-Pro-amide resulted in an increase in plasma levels of the thyroid hormone T3 in normal female mice but did not significantly alter levels in normal males. Moreover, pGlu-Glu-Pro-amide failed to increase T4 in normal females and actually decreased T4 in normal males. T4 levels in normal vehicle-treated female mice was 55.05 nmol/l and after pGlu-Glu-Pro-amide, levels were 48.15 nmol/l. T4 levels in normal vehicle-treated male mice were 44.24 nmol/l and after pGlu-Glu-Pro-amide, levels were 33.45 nmol/l - a statistically significant decrease.

Cremades, in fact, might be cited to support a claim that pGlu-Glu-Pro-amide has less effect on the thyoid axis than does TRH. In fact, Pekary et al. (Brain Research, 2000) report that pGlu-Glu-Pro-amide does not bind to the TRH receptor and does not elevate serum T3 levels at 250 times an effective dose of TRH.

More importantly, however, Cremades et al. teaches nothing about the capacity of pGlu-Glu-Pro-amide to reach or affect central nervous system structures. Applicants' invention teaches the use of pGlu-Glu-Pro-amide as a neuroprotectant in brain, spinal cord and retina. To do so, an agent must reach those structures. Cremades has only shown that the compounds may have reached and acted on the pituitary gland, which is outside the blood brain barrier. It teaches nothing about formulations necessary for administering a compound to the central nervous system, or any part thereof.

Hence, Cremades does not anticipate the present invention under 35 U.S.C. 102(b).

Reconsideration is respectfully requested.

Respectfully submitted,

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Versions with markings to show changes made.

IN THE SPECIFICATION:

Page 1, line 8, please replace pGLU-GLU-PRO-NH^2 with --- pGLU-GLU-PRO-NH_2, both occurrences---.

Page 7, lines 3 and 4, please replace pGLU-GLU-PRO-NH^2 with --- pGLU-GLU-PRO-NH_2---, both occurrences.

Page 10, line 22, please replace pGLU-GLU-PRO-NH^2 with --- pGLU-GLU-PRO-NH_2---.

Page 13, line 1, replace [EEP] with ---EEP---.
lines 5 and 6, delete "What is this appendixx and should it be attached? Where are figs. 1 and 2?."

IN THE CLAIMS:
Please cancel claims 2, 4, 6.

Please amend the claims as follows:

1. (Amended) A pharmaceutical composition comprising a neuroprotectant [pGLU-GLU-PRO-NH^2] amount of pGLU-GLU-PRO-NH_2 as an active ingredient.

3. (Amended) A pharmaceutical composition comprising [pGLU-GLU-PRO-NH^2] pGLU-GLU-PRO-NH_2 and N-tert-Butyl-α-(2-sulfophenyl)nitrone as active ingredients.

5. (Amended) A pharmaceutical composition comprising [pGLU-GLU-PRO-NH^2] pGLU-GLU-PRO-NH_2 and one or more nitrones as active ingredients.

7. (Amended) A method of treating [and/or preventing] neurological diseases and injuries comprising administering to a patent a composition comprising a therapeutically effective amount of [pGLU-GLU-PRO-NH^2] pGLU-GLU-PRO-NH_2 as an active ingredient under time and conditions to treat said disease.

10. (Amended) A method of treating neurological diseases and injuries comprising administering to a patient a composition comprising a therapeutically effective amount of (a) [pGLU-GLU-PRO-NH^2] pGLU-GLU-PRO-NH_2 and (b) N-tert-Butyl-α-(2-

sulfophenyl) nitrone or [other] a free radical scavenging nitrone that enhances the effects of pGLU-GLU-PRO-NH_2 under time and conditions to treat said disease.

---11. (New) A method of preventing neurological diseases and injuries comprising administering to a patent a composition comprising a therapeutically effective amount of pGLU-GLU-PRO-NH_2 as an active ingredient under time and conditions to treat said disease.---.